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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/454,223	12/09/1999	RICHARD S. KORNBLUTH	SD9-003-1	3505

7590 04/17/2007

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EXAMINER	
WOODWARD, CHERIE MICHELLE	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/454,223	KORNBLUTH, RICHARD S.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9-28* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 9-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,16-21,23 and 25-28* is/are rejected.

7)☒ Claim(s) *22, 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Examiner of your Application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this Application should be directed to Cherie Woodward, Art Unit 1647.

Formal Matters

2. Applicant's Response and Amendments filed 29 January 2007 are acknowledged and entered. Claims 1-7 and 9-28 are pending. Claim 8 has been cancelled by Applicant. Claims 1-6 and 9-15 are withdrawn from consideration as being drawn to non-elected inventions pursuant to 37 CFR 1.142(b). Claims 7 and 16-28 are under examination.

Claim Objections

3. Claims 7, 25, and 26 are objected to because of the following informalities: claim 7, line 16, subpart (ii) recites "replacement of the CDR with the ECD..." It appears from the context of the claim and subpart (i) that the "CDR" should be the "CRD" as in "carbohydrate recognition domain." Claim 25 line 2, recites "CD27L/CD70L..." It appears that it should read "CD27L/CD70." Similarly, claim 26 recites "SPD-CD27L/CD70L..." It appears that it should read "SPD-CD27L/CD70." Appropriate correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 7, 16-21, 23, and 27-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the exemplified fusion protein comprising human and murine SPD-CD40L, the exemplified fusion protein comprising murine SPD-RANKL/TRACE, and the exemplified fusion protein comprising SPD-CD27L/CD70, does not reasonably provide enablement for the genus of soluble multimeric polypeptides of at least two trimer units wherein each trimer unit comprises a fusion protein trimer strand consisting of a first polypeptide comprising the first about 100 to 250 N-terminus residues of a collectin family scaffold protein wherein the first polypeptide comprises a

hub and a body region of the collectin family scaffold protein, a second polypeptide comprising the last about 100 to about 250 C-terminus residues of a TNFSF ligand wherein the second polypeptide comprises an extracellular domain (ECD) of the TNFSF ligand, wherein the carboxy-terminal residue of the first polypeptide is operably linked to the amino-terminal of the second polypeptide via (i) the deletion of a carbohydrate recognition domain (CRD) of the collectin family scaffold protein and (ii) replacement of the CDR with the ECD of the TNFSF ligand, whereby a single trimer strand spontaneously trimerizes with two additional trimer strands to form a trimer unit and the trimer unit binds at the hub to form a multimeric polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is drawn to a genus of multimerizing fusion polypeptides wherein the fusion protein comprises a TNFSF member and a collectin family scaffold protein.

The state of the art discloses that the TNF superfamily (TNFSF) includes CD40L, GITRL, RANKL, OX40L, 4-1BBL, LIGHT, CD70, and at least 12 other molecules (see Bodmer et al., Trends Biochem. Sci. 27:19-26). CD40L (also called CD154) has special importance as an initiator and promoter of the immune response (see Kornbluth, J Hematother Stem Cell Res. 2002 Oct;11(5):787-801, Abstract Only). CD40L is considered to be the molecular embodiment of the help provided by activated $CD4^+$ T cells in that it assists dendritic cells in the presenting processed antigen to $CD8^+$ T cells (see Schoenberger et al., Nature. 1998 Jun 4;393(6684):480-3., Abstract Only).

Hoppe et al., (FEBS Lett. 1994 May 16;344(2-3):191-5) teach a parallel three stranded alpha-helical bundle at the nucleation site of collagen triple-helix formation. Hoppe et al., disclose a short stretch of 35 amino acids is identified as the structural motif responsible for the tight parallel association and trimerization of the three identical polypeptide chains of lung surfactant protein D, which contains both collagen regions and C-type lectin domains (Hoppe et al., *supra*, abstract). This 'neck-region' is located at the nucleation site at which the collagenous sequences fold into a staggered triple-helix and is shown, by CD, NMR, and cross-linking of recombinant peptides, to consist of a triple-stranded parallel α-

helical bundle in a non-staggered, and extremely strong, non-covalent association. This type of association between three polypeptide chains may represent a common structural feature immediately following the C-terminal end of the triple-helical region of collagenous proteins (Hoppe et al., *supra*, abstract).

The level of skill of those in the art is drawn to protein chemistry related to recombinant fusion protein constructs and determination of biological activity of fusion proteins. The skill level needed to construct fusion proteins is high due to the multifactorial parameters necessary to generate the constructs and determine biological function.

The guidance provided in the specification is not commensurate in scope with the claims, as written. Claim 7, for example, is broadly directed to a family of TNFSF ligands and to collectin family scaffold protein members. Table I and II of the specification (pp. 35, 36) disclose non-limiting examples of TNFSF ligands and collectin family scaffold proteins, respectively. However, the specification also states that the TNFSF superfamily consists of an expanding number of proteins which are expressed as Type II membrane proteins, with the exception of lymphotoxin-alpha, which is produced as a secreted protein (see especially, p. 2, last line to page 3, first paragraph). The guidance provided on pages 2-3 of the specification is not commensurate in scope with claim 7, as written. It is unclear how one of skill in the art is to discern what structural protein constitutes a TNFSF ligand family member. Using Applicant's definition of TNFSF member on pages 2-3 of the specification, it would have to be a Type II membrane protein. However, there are exceptions to this requirement that are set forth, but the exceptions are not limited. The disclosure that soluble forms of other TNFSF proteins can be released from the cell surface by proteolytic cleavage, usually by specific metalloproteinases, expands the scope of potential TNFSF proteins that are relevant to claim 7, for example. However, the specification fails to provide any specific guidance on what structural requirements are necessary in order for any particular polypeptide to meet the limitations of the claims. Based on the teachings in the specification, one of skill in the art would not be able to clearly ascertain whether any particular polypeptide fell within Applicant's definition of "TNFSF member" such that it would be encompassed within the scope of the claims, as written. Additionally, the question of functionality of soluble TNFSF family members is raised in the specification on page 4, last two lines to page 5, first paragraph. It is unclear from the guidance provided in the specification, which soluble TNFSF members will actually work for the intended purpose of stimulating B-cells.

There is even less guidance in the specification as to which polypeptides comprise the genus of collectin family scaffold members. The specification teaches that all collectins are formed as multimers if

trimeric subunits, each containing a collagenous domain (p. 36, first paragraph). The specification also gives some very basic structural information as to the carbohydrate binding domain of collectins, but does not otherwise clearly define any other collectins, other than those specifically listed in Table II. It is unclear from the guidance provided in the specification is the listing in Table II is intended to be limiting or whether other unspecified collectin superfamily members are to be encompassed within the scope of the claims.

The claims do not begin to define structural limitations of TNFSF family members until you get to claim 16, for example, which begins to recite specific polypeptides with known, defined structure. The TNFSF polypeptides listed in claim 16 are exemplified in Table 1, page 35 of the specification. Similarly, the collectin family scaffold proteins of claim 17 are exemplified in Table II, page 36 of the specification. However, because claim 7 recites a fusion protein it is necessary that the structural components of both parts of the fusion protein be known or defined with certainty. Otherwise, one of skill in the art will be unable to make or use Applicant's invention in its full scope.

Therefore, based on the discussions above concerning the art's recognition that knowing the structure of a polypeptide is important because differences in structure will often dramatically affect the biological activity, due to the lack of guidance in the specification, one of skill in the art would not be able to predictably make and use the claimed genus of polypeptides comprising TNFSF/collectin family scaffold fusion proteins to make the recited protein complex, as claimed. Thus, it would require undue experimentation by one of skill in the art to make, use, or practice the invention as claimed in its full scope.

Claim Rejections - 35 USC § 112, Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 7, 25, and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7, line 16, subpart (ii) recites "replacement of the CDR with the ECD..." It appears from the context of the claim and subpart (i) that the "CDR" should be the "CRD" as in "carbohydrate recognition domain." However, Applicant could be referring to something else by referring to "CDR". This is confusing and clarification is required.

The subject matter of claims 25 and 26 is confusing. Claim 25 line 2, recites "CD27L/CD70L..." Similarly, claim 26 recites "SPD-CD27L/CD70L..." By reciting CD27L/CD70L, it appears that

Applicant is intending the claim to encompass two entirely different proteins. CD27L is also known in the art as CD70 (but not CD70L, which is an entirely different protein) (see Table I, p. 35 of the specification). If the "CD70L", referred to in claims 25 and 26 are only typographical errors, appropriate correction is requested in order to clarify what Applicant actually intends.

Conclusion

8. Claims 22 and 24 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 7, 16-21, 23, 25-28 are rejected.

This action is Non-Final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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